A cross-section Study of Sleep Apnea Prevalence in the General Population age 71 years and its association with cardiovascular disease

30 hp Master thesis in Medicine

Name of Student: Stefano Garcia Sahlgrenska Academy, University of Gothenburg

Primary Supervisor: Erik Thunström MD, PhD,
Dept of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg
Secondary Supervisor: Michael Fu, MD, PhD, FESC, Dept of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

Gothenburg, Sweden 2015

Abstract

Background: There is a lack of knowledge regarding obstructive sleep apnea (OSA) prevalence in older men from the general population. The aim of this cross-sectional study was to determine the prevalence of OSA in 71-year old men derived from the general population in Gothenburg, Sweden. Moreover, to study if OSA, is associated with cardiovascular diseases and if it is more common than other cardiovascular risk factors in this population.

Material and Methods: This study is based on men who participated in the re-examination, in 2014, of participants from the "The study of men born in 1943". All participants answered questionnaires on health status, quality of life. They were than examined at Sahlgrenska University Hospital/Östra in Gothenburg, Sweden, in addition sleep-apnea screening and thumb-EKG was performed in the participants' homes.

Results: A total 536 participants were included in our database, 412 of those underwent sleep-apnea screening and were eligible for this study. 121 had obstructive sleep apnea (OSA), with AHI (apnea-hypopnea index) ≥ 15/h, and 191 did not. Thus, OSA (AHI ≥ 15) is common in the old general population. Moreover, it is the second most common risk factor for CVDs after hypertension in this population. The prevalence of OSA was 29.4% in this study. BMI showed significance with OSA (AHI ≥ 15). We found that sleep-disordered breathing is associated with prevalence of hypertension in older men; however after adjustment for BMI the association was no-longer significant. In the subgroup of patients with severe OSA (AHI ≥30) an association could be found between severe OSA and atrial fibrillation even after adjustment for BMI, OR 2.43 (1.02-5.76)

Conclusions: Obstructive sleep apnea (OSA) is common in the old general population. There is a more than two fold risk increase for having atrial fibrillation among those that had sever OSA. Longitudinal studies on older general population is warranted to establish whether OSA is a risk factor for development of atrial fibrillation as well as other cardiovascular disease for all individuals and not only for those in certain disease cohorts or for those with day-time sleepiness.

Table of Contents

Background

The prevalence of Obstructive sleep apnea (OSA) in the population varies greatly depending on what definitions for OSA that have been used. Young et al. did publish a paradigm shifting work in 1993 where they found that the prevalence of OSA in middle aged (30-60 years old) individuals from the general population were 9% for women and 24% for men, defining OSA as having apnea-hypopnea index (AHI) ≥ 5 independent of daytime sleepiness[1]. OSA can be divided into mild (AHI 5-15/h), moderate (AHI 15-30/h) or severe (AHI > 30/h)[2]. To be called apnea the loss of airflow in the upper airways (nose and mouth) must have a duration of more than 10 seconds, hypopnea on the other hand must result in a desaturation of ≥ 4% or ≥3% depending on what guidelines are used, for example the 2012 update of the 2007 guideline from AASM (American Academy of Sleep Medicine)[3, 4].

The frequent apneas during sleep in people with OSA occurs when the motor tone of the airway dilator muscles or the tongue (or both) is inadequate and therefore leads to the obstruction of the upper airway[3, 5]. CPAP (continuous positive airway pressure) is first line treatment. It opens the upper airways and thus improves the quality of sleep which leads to less subjective daytime sleepiness. In studies, compliance to treatment is considered to be a minimum of 4 hours CPAP use[6-8]. It is known that OSA is an independent risk factor for cardiovascular diseases such as stroke[9], heart failure and arterial hypertension[10-12]

But there is a lack of knowledge regarding obstructive sleep apnea (OSA) prevalence in older men, over 70-years of age, from the general population. There are two major studies, the one mentioned above by Young et al.[1] and The Sleep Heart Health study (males ≥ 40 years)[13], where they investigate OSA in people from the general population. But they do not only investigate men ≥ 70 years old.

With this study we want to fill this gap in knowledge. Because of the large number of participants in this study we used ApneaLink™ (a portable sleep-screening tool) in our OSA screening[14]. It was not practically possible for us to use overnight Polysomnography (PSG). In this sub-study we use a cut-off at AHI ≥ 15/h for OSA.

Usually OSA is defined both by Polysomnography (PSG) finding, e.g. AHI ≥ 5 and clinical signs of OSA (which includes symptoms like recurrent awakenings, fatigue or inability to focus, choking at night and a sensation of non-restorative sleep; two of these symptoms or excessive daytime sleepiness is needed for diagnosis) and is then called OSA-syndrome [3, 6, 15, 16]. However, a minority of all that suffer from OSA (e.g. AHI ≥ 5) suffer from daytime sleepiness[1]. OSA can also be defined by AHI ≥ 15/h without any disorders or symptoms[17].

There are two main branches of apnea, central sleep apnea (CSA) and obstructive sleep apnea (OSA)[2]. They both overlap, and we know that there is not sufficient data on the prevalence of central sleep apnea in the general population[18]. As mentioned above, if a person suffers from excessive daytime sleepiness and at the same time have OSA it's called obstructive sleep apnea syndrome (OSAS)[19, 20]. In middle-aged people from the general population a connection between OSA and several cardiovascular diseases has been observed: hypertension[21, 22]; ischemic stroke (threefold increased risk in men with moderately severe OSA)[23]; coronary heart disease were men in the age of 40-70 years and with an AHI ≥ 30 have 68% increased risk to develop compared to individuals from the same population with AHI < 5)[24]; heart failure which males 40-70 years of age and AHI ≥30 have 58% increased risk to develop compared individuals from the same group with an AHI < 5)[24]; and atrial fibrillation. According to a study from 2007 OSA is an independent risk factor for AF in people < 65 years of age but not for those ≥ 65[25], another study from 2009 supports that (the mean age of the participating community-dwelling males in that study were 76,4 years) because an association between CSA and AF was found but not between AF and OSA in older men[26]. The association between OSA and CVDs is strongest amongst those of middle-age with severe OSA (AHI > 30), but not so amongst those of older age. But according to an article from 2009, the Sleep Heart Health Study, sleep-disordered breathing is not, after adjusting for BMI, an independent risk factor for hypertension in middle-age and older men[27]. OSA can also by itself cause pulmonary hypertension[10]. Obesity is the largest predisposing factor to develop OSA, another important trigger factor is alcohol. Risk factors for developing CVDs are OSA[11, 12], obesity[28, 29], hypertension[30-32], type 2 diabetes mellitus[33], lack of physical activity[34], hyperlipidemia[35], high cholesterol[22] and smoking[22, 33]. Other risk factors for CVDs according to the World Heart Federation are harmful use of alcohol, unhealthy diet, ethnicity, age, gender and family history[36, 37].

The cohort “The study of men born in 1943” is in the layup a copy of the “The study of men born in 1913”. Every ten years, in a cross-section of the population in Gothenburg, the mortality and the comorbidities are investigated in these studies: risk factors; diseases; cancer; CVDs. In 1993 participants of “The study of men born in 1943” was examined for the first time, they had a follow-up in 2003 and was last examined in 2014 instead of in 2013.

This article is based on that latest examination, which was the most comprising as of yet, and is a sub study with the aim to investigate the prevalence of OSA (cut-off at AHI ≥ 15) in community-dwelling 71-year old men in Gothenburg (Sweden) and to see if OSA is associated with cardiovascular diseases in these participants. Another aim is to compare OSA to the prevalence of other risk factors for CVDs such as hypertension, type 2 diabetes mellitus, smoking and obesity.

Aim/specific objectives/research question

The primary aim of this study is to measure the prevalence of obstructive sleep apnea (OSA) in 71-year old men from the general population in Gothenburg, Sweden. The secondary aim is to see if OSA, is associated with cardiovascular diseases in participants over 70 years of age. The tertiary aim is to see if OSA is more common than other cardiovascular risk factors in this study population.

We hypothesizes that OSA is more common in this older population than what have been observed in younger cohorts[1]. Moreover, we assume that OSA is associated with cardiovascular disease (e.g. hypertension atrial fibrillation, coronary artery disease and heart failure) in this older population. The following research questions were therefore stipulated: ”What is the prevalence of obstructive sleep apnea in 71-year old men from the general population?”, ”Is OSA associated with cardiovascular disease?” and “Is OSA more common than other cardiovascular disease risk factors?”.

Material and Methods

Study population

This sub-study is based on the data collected during the third follow-up examination, in 2014, of the participants of the main study "The study of men born in 1943" which started in 1993. In 1993, a random sample from the population, in Gothenburg (Sweden), was selected. The criteria, for participation in the study, were male gender, date of birth during 1943 (50 years of age) and a resident of Gothenburg. Every second person fulfilling this criteria were randomly selected and invited to participate in the study, a total of 1460 men were summoned. Of those 6 was diseased and 1 had immigrated and they were therefore excluded. A total of 1453 were thus eligible for part taking in the study at the first visit in 1993, of those 656 people declined or did not respond to the first summon. Thus, 54.9% (n = 798) participants were examined in 1993. A re-examination was performed in 2014. Of the 798 participants examined in 1993 15.2% or 121 had diseased 2014 and 3.0% or 24 people had emigrated, had an unknown address, or had changed sex (n = 1) during the follow-up period. Thus, 653 men were invited to the reexamination, the criteria for participation was that they had been examined in 1993. Of those 6.6% (n =43) people did not want to, or could not participate and 11.3 % (n =74) people did not answer the call for reexamination, consequently a total number of 536 participants, 67.2% of those originally examined were reexamined between 2014-05-14 and 2014-12-15.

Examinations

Before physical examination each participants received three different questionnaires: a WHO-form about physical activity, smoking habits, chest pain and levels of stress; a questionnaire addressing medical history and the third questionnaire focused on eating habits. The research division at Sahlgrenska University Hospital Östra in Gothenburg (Sweden) performed all the examinations. The participants born earliest during the year were summoned first. The participants should not have eaten or used any tobacco products for at least four hours prior to the examination. The examination included collection of venous blood samples (S-cholesterol, S-triglycerides, HDL-cholesterol, LDL-cholesterol, fasting-plasma-glucose, NT-proBNP), echocardiography, EKG, anthropometric data (length, hip, waist, weight, upper right arm), blood pressure, heart and lung auscultation, checking for signs of heart failure, angina pectoris, intermittent claudication and a part of Berg's balance scale test. The only examinations not performed directly were the sleep apnea screening (offered to participants without known sleep apnea) and thumb EKG. The participants received (after the examination at the hospital) a portable ApneaLink™ Plus (Resmed, San Diego, Ca, USA) for the apnea screening and thumb EKG-machine (Zenicor-EKG, Zenicor Medical Systems AB, Stockholm, Sweden) to take home. (For the first two months we used ApneaLink™ which cannot differentiate between CSA and OSA.) The participants who accepted the ApneaLink™ Plus screening used it for one home-night-sleep were also answering a questionnaire regarding sleep and sleep disorders, as well as the Epworth Sleepiness Scale. The thumb EKG was used two times a day for two weeks. It was first after the participants came back with the equipment that the data stored in them could be read. The examinations were carried out by healthcare professionals; this included cardiologists, doctors, a nurse, an assistant nurse and two medical school students (five years into their education). The blood samples were analyzed at Sahlgrenska University Hospital in Gothenburg (Sweden).

Data collection procedures

All the data from the eleven forms used in the main study were entered into a Microsoft Excel 2010 document and proofread by medical school students (S.G. and H.H.H). All the original forms are stored at Sahlgrenska University Hospital Östra in Gothenburg, Sweden.

Bias

Although the option to participate in the main study for the first time in 1993 was given to men born in 1943 and at the time of the study start lived in Gothenburg many of them declined. A major similar study from the general population has shown that there is a large difference in participation rates between people from areas of low and high socio-economic status, only 37% participation rate regarding the low socio-economic status area compared to 67% from the high socio-economic status area[38]. We suspect that many of the people who accepted our invitation to participate in the main study in 1993 were those of a relatively higher socioeconomic status and better health. It is possible that this can be a source of selection bias.

Variables

The variables used in this sub-study are taken from the forms mentioned above. The main out-come variable is OSA, defined using an AHI cut-off $\geq$ 15/h. The cut-off used was the cut-off for moderate OSA, which also is the level required to obtain CPAP treatment at Sahlgrenska University Hospital. Furthermore, the ApneaLink™ has a god sensitivity and specificity for detecting OSA at this AHI cut-off[14] . Other variables used in the analyses are hypertension, type 2 diabetes mellitus, smoking and obesity. Age and gender are not relevant in the analyses since all the participants were born in 1943 and all are males. Body max index (BMI) $\geq$ 30 kg/m^2 equals obesity and the formula used to calculate BMI was bodyweight divided by height squared. Hypertension is defined as a systolic blood pressure of $\geq$140 and/or a diastolic blood pressure of $\geq$90, and/or if a doctor has diagnosed high blood pressure and/or if a participant is taking medication for hypertension.

Statistical methods

Linear regression analysis was used to analyze correlations between continuous variables while logistic regression analysis was used to analyze correlations between categorical variables. All p-values below 0.05 were considered significant. The Statistical Package for Social Sciences version 22.0 for the Windows system (SPSS Inc., Chicago, IL) was used to perform all the statistical analysis. For comparison of the groups, Independent sampled student T-test and Cross Tabulation were used. Chi-square test was applied for comparison of the categorical variables.

Ethics

All the participants in this study were part of it on their own free will. They could at any given time discontinue their participation in the study. All participants were given written and oral information and signed informed consent. If a disease or symptom were detected during the examinations it was addressed according to clinical routines at the hospital.

This study complies with the UNESCO´s "Universal Declaration on Bioethics and Human Rights"[39] and the World Medical Association's "Declaration of Helsinki "[40], and the study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Gothenburg.

Results

We invited 653 participants to our main study "The study of men born in 1943". Of those 536 participants came to be examined and were included in our database (Figure 1). 412 had filled in the required questionnaires and participated in sleep apnea screening and were thus eligible for this sub-study. 121 had obstructive sleep apnea (OSA), with cutoff at AHI (apnea-hypopnea index) ≥ 15/h, and 291 did not.

Table 1: Of all the variables, except "AHI" and "ODI", only "Obesity", "BMI", ", "Heart failure" and "Hypertension" showed a significant difference between the groups.

The univariate logistic regression analysis shows that the univariate variables "BMI", "Obesity" and "Hypertension" were associated with OSA (Table 2) in this cross-sectional sub-study. In the multivariate logistic regression analysis (Table 2) only BMI showed a significant association with OSA.

The prevalence of conditions and diseases in the study population:

As shown in Figure 2, OSA is highly prevalent in the cohort. Moreover it has a higher prevalence in the cohort than most risk factor for CVDs and it is more common than atrial fibrillation, myocardial infarction, angina, chronic obstructive pulmonary disease (COPD) and heart failure.

Figure 3 shows the occurrence of CVDs and risk factors of those with OSA, cutoff AHI ≥ 15. When looking at only the OSA population there is a 10.7% increase in the prevalence of hypertension compared to the study population who do not have OSA (Figure 4). A 19.5% increase regarding obesity. There is also an increase in atrial fibrillation (6.1%), diabetes (4.0%), myocardial infarction (3.5%), angina (1.8%) and heart failure (3.7%). But there is a decrease in the prevalence of stroke (3.8%), current smoking (0.3%) and COPD (1.9%) compared to the no-OSA population.

Figure 4 shows the occurrence of CVDs and risk factors of those who do not have OSA. As stated above it is more common with stroke, COPD and current smoking compared to the study population that has OSA (Figure 3).

Figure 5 shows the different AHI levels in the study population n=412. 138 people or 33.5% were within the AHI interval 0-4.99. 153 or 37.1% in AHI 5-14.99. 85 or 20.6% in AHI 15-29.99. 36 or 8.7% had AHI $\geq$ 30. ApneaLink™ is not verified regarding AHI < 15 and thus we will not use the intervals below the cut-off for this study. A total of 70.6% of the participants had AHI below 15 and 29.4% had above.

Table 3 shows the characteristics of the study population with severe obstructive sleep apnea. “Obesity”, “BMI”, “Hypertension” and “Atrial fibrillation” shows significance with severe OSA.

Table 4 shows variables associated with severe obstructive sleep apnea. The univariate analysis shows significance between “Obesity”, “BMI”, “Atrial fibrillation” and “Hypertension”. In the multivariate analysis only BMI and atrial fibrillation remained significant with severe OSA. A 2.4 odds ratio regarding “Atrial fibrillation” could be seen.

Figure 6 shows the occurrence of CVDs and risk factors of those with severe OSA, cutoff AHI $\geq$ 30. The prevalence of hypertension in this study population (n = 36) is very high (97.2%). The occurrence of obesity, atrial fibrillation and diabetes is also very common.

Discussion

In this sample of 71-year old men we have found that OSA (AHI ≥ 15) is common in the old general population. Moreover, it is the second most common risk factor for CVDs after hypertension. An association could be found between severe OSA and BMI and atrial fibrillation (Table 4). Table 4 also shows that it is 2.4 times increased risk to have atrial fibrillation if you have severe OSA. The prevalence of OSA is 29.4% among old men (71 years) in this study. A flow chart of the participants shows that 412 of them met the requirements needed to be a part of this sub-study (Figure 1). The flow chart lists various reasons why participants were excluded. Maybe these exclusions affected the prevalence of moderate to severe OSA in the study population. Young et al[1] showed a prevalence of OSA by 24% (cut-off AHI ≥ 5) among males in their study population which consisted of middle-aged (30-60 years old) individuals from the general population. It is important to note that we used a different cut-off (AHI ≥ 15) for OSA than they did in the study mentioned above.

We found that among 71-year-old males OSA is not only more common than typical CVDs risk factors such as obesity, type 2 diabetes mellitus and smoking but also more prevalent than atrial fibrillation, myocardial infarction, angina pectoris and chronic obstructive pulmonary disease (COPD).

The multivariate logistic regression analysis in Table 2 shows that there was only significance in the association between OSA and BMI. The results in this study is similar as what was found in the Sleep Heart Health Study 2009, that sleep-disordered breathing not is, after adjusting for BMI, an independent risk factor for hypertension in older men[27]. But in their study there wasn't even an association in middle-aged men.

Table 1 support our hypothesis, that obstructive sleep apnea is more common in this older population compared to cohorts with younger people[1]. And we even used a much higher cut-off at AHI ≥ 15. The hypothesis is therefore relevant, a new hypothesis could be “Is the prevalence of OSA in the general population age dependent and is it clinically relevant after adjusting for age?”.

It was more common that the participants with OSA had hypertension, obesity, diabetes, higher BMI, higher ESS score, atrial fibrillation, heart failure, myocardial infarction, angina pectoris and cancer compared to the “no OSA group”. More participants of the OSA group had also in greater extent undergone bypass surgery and PCI (Percutaneous coronary intervention). Although most of these differences between the two groups were not significant.

Even though the awareness of OSA has increased, compared to other cardiovascular risk factors such as diabetes it is still an underestimated condition and its association with cardiovascular diseases needs to be further explored especially in non-sleep laboratory cohorts.

Sleep is an important part of life, some sleep more and some less, and maybe an early detection of OSA in people with symptoms (through sleep-screening at their homes) could lead to health benefits through early treatments and therefore lowering the total costs of healthcare which in the end mean socio-economic gains.

The strength of this study lies in the fact that the study population is very homogenous (same sex and of the same age) and from the general population, unlike many other studies in which the study population consists of hospital patients.

A limitation to this study is that the study population could be a source of selection bias[38]. Why that is could have its answer in that people of a relatively higher socioeconomic class tends to participate in this kind of studies. Maybe they also take care of themselves better, read more about different lifestyle related diseases and what to do to avoid them and that they are more positive to participate in studies like this. Because they participate in studies who offer health care examinations for free there is an opportunity for discovery of serious symptoms and diseases by chance. The participants therefore receive treatment for serious symptoms and diseases much earlier than those who choose not to participate; treatments that in many cases could be directly lifesaving. Another limitation to this study is that we did not use overnight Polysomnography (PSG) in the detection of OSA. PSG is more sensitive than ApneaLink™ at lower AHI levels[14]. If we had used PSG and cut-off for OSA at AHI ≥ 5 the prevalence of OSA would probably have been higher.

Conclusion

Obstructive sleep apnea (OSA) is common in the old general population, 29.4%. BMI is associated with OSA (AHI ≥ 15). There is a more than two fold risk increase for having atrial fibrillation among those that had sever OSA. As a risk factor for CVDs OSA was the second most common after hypertension. A possible association could be found between OSA and hypertension in this study, but after adjusting for BMI the association was no longer significant. Longitudinal studies on older general population is warranted to establish whether OSA is a risk factor for development of atrial fibrillation as well as other cardiovascular disease for all individuals and not only for those in certain disease cohorts or for those with day-time sleepiness. More questionable is whether OSA is associated to most of the CVDs.

Populärvetenskaplig sammanfattning

Sömnapné eller andningsuppehåll då man sover är mycket vanligt hos äldre personer i befolkningen och deltagarna i denna understudie tillhörde denna kategori. Den sortens sömnapné som vi här berör är den obstruktiva eller tilltäppande/hindrande sömnapnén. Precis som man hör på namnet innebär detta en tilltäppning av luftvägarna, i detta fall av svalget då tungan under sömnen glider bakåt och på så sätt hindrar luftflödet under andningen. Andningsrörelserna fortsätter men otillräckligt med syrerik luft åker ned och fyller lungorna. Det kan leda till att man inte blir utsövd och därför är trött under dagen samt har koncentrationsproblem. Sömnapné är vanligare hos feta individer och hos de som brukar alkohol innan sänggående. Alkoholen gör att muskler i svalget slappnar av vilket kan leda till ett trängre utrymme för luften att passera. Om man har tillräckliga besvär kan man få behandling med en så kallad CPAP-apparat, CPAP är en engelsk förkortning på Continuous Positive Airway Pressure vilket är kontinuerlig övertrycksbehandling på svenska.

Många artiklar har tidigare skrivit att sömnapné i sig självt leder till för högt blodtryck, vi fann att ett sådant samband i den äldre manliga delen av befolkningen möjligen kan finnas. Med äldre menar vi personer över 70 år. Vi kunde inte finna något samband mellan sömnapné och de flesta av hjärt- och kärlsjukdomarna. Men hos de med allvarlig obstruktiv sömnapné fann vi ett samband med BMI (Body Mass Index) och förmaksflimmer.

Vi fann att sömnapné inte bara är mer vanligt förekommande än fetma och rökning utan också mer vanligt än förmaksflimmer, hjärtinfarkt, hjärtsvikt, kronisk obstruktiv lungjukdom och diabetes. Det man kan fundera på är om sömnapné är en del i det naturliga åldrandet och vilka sjukdomar detta kan leda till hos den drabbade.

Sömnen är ett mycket viktigt område då vi alla tillbringar en stor del av livet sovandes, andra mer och andra mindre. I samband med att vi blir allt äldre och fetare kommer förmodligen fler personer drabbas av sömnapne. Därför tycker vi att konsekvenserna av andningsuppehåll under sömnen och dess samband med hjärt- och kärlsjuklighet borde utredas vidare.

Kanske kan en tidig upptäckt av sömnapné hos folk med symptom leda till hälsovinster för den enskilde genom att de får tidig behandling vilket i sin tur skulle leda till samhällsekonomiska vinster genom att de totala sjukvårdskostnaderna då sjunker.

Vi tycker att denna studien är viktig eftersom den visar hur vanligt sömnapné är hos äldre män från den vanliga befolkningen.

Undersökningarna av deltagarna ägde rum på Sahlgrenska Universitetssjukhuset/Östra mellan 2014-05-14 och 2014-12-15. Deltagarna fick med sig hem en liten apparat (heter ApneaLink™) som mäter andningsuppehåll och en annan apparat som mäter pulsen genom att man fäster den på tummen.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S and Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *The New England journal of medicine*. 1993;328:1230-5.
2. Floras JS. Sleep apnea and cardiovascular risk. *Journal of cardiology*. 2014;63:3-8.
3. Park JG, Ramar K and Olson EJ. Updates on definition, consequences, and management of obstructive sleep apnea. *Mayo Clinic proceedings*. 2011;86:549-54; quiz 554-5.
4. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL and Tangredi MM. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2012;8:597-619.
5. Dempsey JA, Veasey SC, Morgan BJ and O'Donnell CP. Pathophysiology of sleep apnea. *Physiological reviews*. 2010;90:47-112.
6. Gagnon K, Baril AA, Gagnon JF, Fortin M, Decary A, Lafond C, Desautels A, Montplaisir J and Gosselin N. Cognitive impairment in obstructive sleep apnea. *Pathologie-biologie*. 2014.
7. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ and Hla KM. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. *WMJ : official publication of the State Medical Society of Wisconsin*. 2009;108:246-9.
8. Tazbirek M, Slowinska L, Kawalski M and Pierzchala W. The rheological properties of blood and the risk of cardiovascular disease in patients with obstructive sleep apnea syndrome (OSAS). *Folia histochemica et cytobiologica / Polish Academy of Sciences, Polish Histochemical and Cytochemical Society*. 2011;49:206-10.
9. Loke YK, Brown JW, Kwok CS, Niruban A and Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. *Circulation Cardiovascular quality and outcomes*. 2012;5:720-8.
10. Dumitrascu R, Heitmann J, Seeger W, Weissmann N and Schulz R. Obstructive sleep apnea, oxidative stress and cardiovascular disease: lessons from animal studies. *Oxidative medicine and cellular longevity*. 2013;2013:234631.
11. Monahan K and Redline S. Role of obstructive sleep apnea in cardiovascular disease. *Current opinion in cardiology*. 2011;26:541-7.
12. Devulapally K, Pongonis R, Jr. and Khayat R. OSA: the new cardiovascular disease: part II: Overview of cardiovascular diseases associated with obstructive sleep apnea. *Heart failure reviews*. 2009;14:155-64.
13. Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redline S, Robbins J, Samet JM and Wahl PW. The Sleep Heart Health Study: design, rationale, and methods. *Sleep*. 1997;20:1077-85.
14. Erman MK, Stewart D, Einhorn D, Gordon N and Casal E. Validation of the ApneaLink for the screening of sleep apnea: a novel and simple single-channel recording device. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2007;3:387-92.
15. G JEAN-LOUIS FZ, DB BROWN, G OGEDEGBE, JS BORER, and SI McFARLANE. Obstructive sleep apnea and cardiovascular disease: evidence

and underlying mechanisms. 2009;Minerva Pneumol. 2009 December ; 48(4): 277–293.
16. Epstein LJ, Kristo D, Strollo PJ, Jr., Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM and Weinstein MD. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2009;5:263-76.

17. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014;146:1387-94.
18. Johansson P, Alehagen U, Svanborg E, Dahlstrom U and Brostrom A. Clinical characteristics and mortality risk in relation to obstructive and central sleep apnoea in community-dwelling elderly individuals: a 7-year follow-up. *Age and ageing*. 2012;41:468-74.
19. Zhang W and Si LY. Obstructive sleep apnea syndrome (OSAS) and hypertension: pathogenic mechanisms and possible therapeutic approaches. *Upsala journal of medical sciences*. 2012;117:370-82.
20. Kielb SA, Ancoli-Israel S, Rebok GW and Spira AP. Cognition in obstructive sleep apnea-hypopnea syndrome (OSAS): current clinical knowledge and the impact of treatment. *Neuromolecular medicine*. 2012;14:180-93.
21. Peppard PE, Young T, Palta M and Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *The New England journal of medicine*. 2000;342:1378-84.
22. Daviglus ML, Talavera GA, Aviles-Santa ML, Allison M, Cai J, Criqui MH, Gellman M, Giachello AL, Gouskova N, Kaplan RC, LaVange L, Penedo F, Perreira K, Pirzada A, Schneiderman N, Wassertheil-Smoller S, Sorlie PD and Stamler J. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. *Jama*. 2012;308:1775-84.
23. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M and Punjabi NM. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *American journal of respiratory and critical care medicine*. 2010;182:269-77.
24. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M and Shahar E. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation*. 2010;122:352-60.
25. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T and Somers VK. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *Journal of the American College of Cardiology*. 2007;49:565-71.
26. Mehra R, Stone KL, Varosy PD, Hoffman AR, Marcus GM, Blackwell T, Ibrahim OA, Salem R and Redline S. Nocturnal Arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study. *Archives of internal medicine*. 2009;169:1147-55.
27. O'Connor GT, Caffo B, Newman AB, Quan SF, Rapoport DM, Redline S, Resnick HE, Samet J and Shahar E. Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. *American journal of respiratory and critical care medicine*. 2009;179:1159-64.
28. He L, Tang X, Song Y, Li N, Li J, Zhang Z, Liu J, Yu L, Xu H, Zhang J and Hu Y. Prevalence of cardiovascular disease and risk factors in a rural district of Beijing, China: a population-based survey of 58,308 residents. *BMC public health*. 2012;12:34.
29. May AL, Kuklina EV and Yoon PW. Prevalence of cardiovascular disease risk factors among US adolescents, 1999-2008. *Pediatrics*. 2012;129:1035-41.
30. Rodriguez-Sanchez E, Garcia-Ortiz L, Gomez-Marcos MA, Recio-Rodriguez JI, Mora-Simon S, Perez-Arechaederra D, Agudo-Conde C, Escribano-Hernandez A and Patino-Alonso MC. [Prevalence of cardiovascular diseases and cardiovascular risk factors in older than 65 years persons in an urban area: DERIVA study]. *Atencion primaria / Sociedad Espanola de Medicina de Familia y Comunitaria*. 2013;45:349-57.
31. Kwon Y, Duprez DA, Jacobs DR, Nagayoshi M, McClelland RL, Shahar E, Budoff M, Redline S, Shea S, Carr JJ and Lutsey PL. Obstructive sleep apnea and progression of coronary artery calcium: the multi-ethnic study of atherosclerosis study. *Journal of the American Heart Association*. 2014;3.

32. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, Martinez-Alonso M, Carmona C, Barcelo A, Chiner E, Masa JF, Gonzalez M, Marin JM, Garcia-Rio F, Diaz de Atauri J, Teran J, Mayos M, de la Pena M, Monasterio C, del Campo F and Montserrat JM. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *Jama*. 2012;307:2161-8.
33. Lorber D. Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus. *Diabetes, metabolic syndrome and obesity : targets and therapy*. 2014;7:169-83.
34. Zhou T, Li X, Tang Z, Xie C, Tao L, Pan L, Huo D, Sun F, Luo Y, Wang W, Yan A and Guo X. Risk factors of CVD mortality among the elderly in Beijing, 1992 - 2009: an 18-year cohort study. *International journal of environmental research and public health*. 2014;11:2193-208.
35. Guallar E, Banegas JR, Blasco-Colmenares E, Jimenez FJ, Dallongeville J, Halcox JP, Borghi C, Masso-Gonzalez EL, Tafalla M, Perk J, De Backer G, Steg PG and Rodriguez-Artalejo F. Excess risk attributable to traditional cardiovascular risk factors in clinical practice settings across Europe - The EURIKA Study. *BMC public health*. 2011;11:704.
36. Federation WH. Cardiovascular disease Risk factors. *World Heart Federation*. 2012.
37. Federation WH. State of the Heart Cardiovascular Disease Report. *World Heart Federation*. 2012.
38. Bergstrom G, Berglund G, Blomberg A, Brandberg J, Engstrom G, Engvall J, Eriksson M, de Faire U, Flinck A, Hansson MG, Hedblad B, Hjelmgren O, Janson C, Jernberg T, Johnsson A, Johansson L, Lind L, Lofdahl CG, Melander O, Ostgren CJ, Persson A, Persson M, Sandstrom A, Schmidt C, Soderberg S, Sundstrom J, Toren K, Waldenstrom A, Wedel H, Vikgren J, Fagerberg B and Rosengren A. The Swedish CArdioPulmonary BioImage Study: objectives and design. *Journal of internal medicine*. 2015;278:645-59.
39. UNESCO. Universal Declaration on Bioethics and Human Rights. 2005.
40. Association WM. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2013

Tables and Figures

Figure 1. Flow chart of the participants

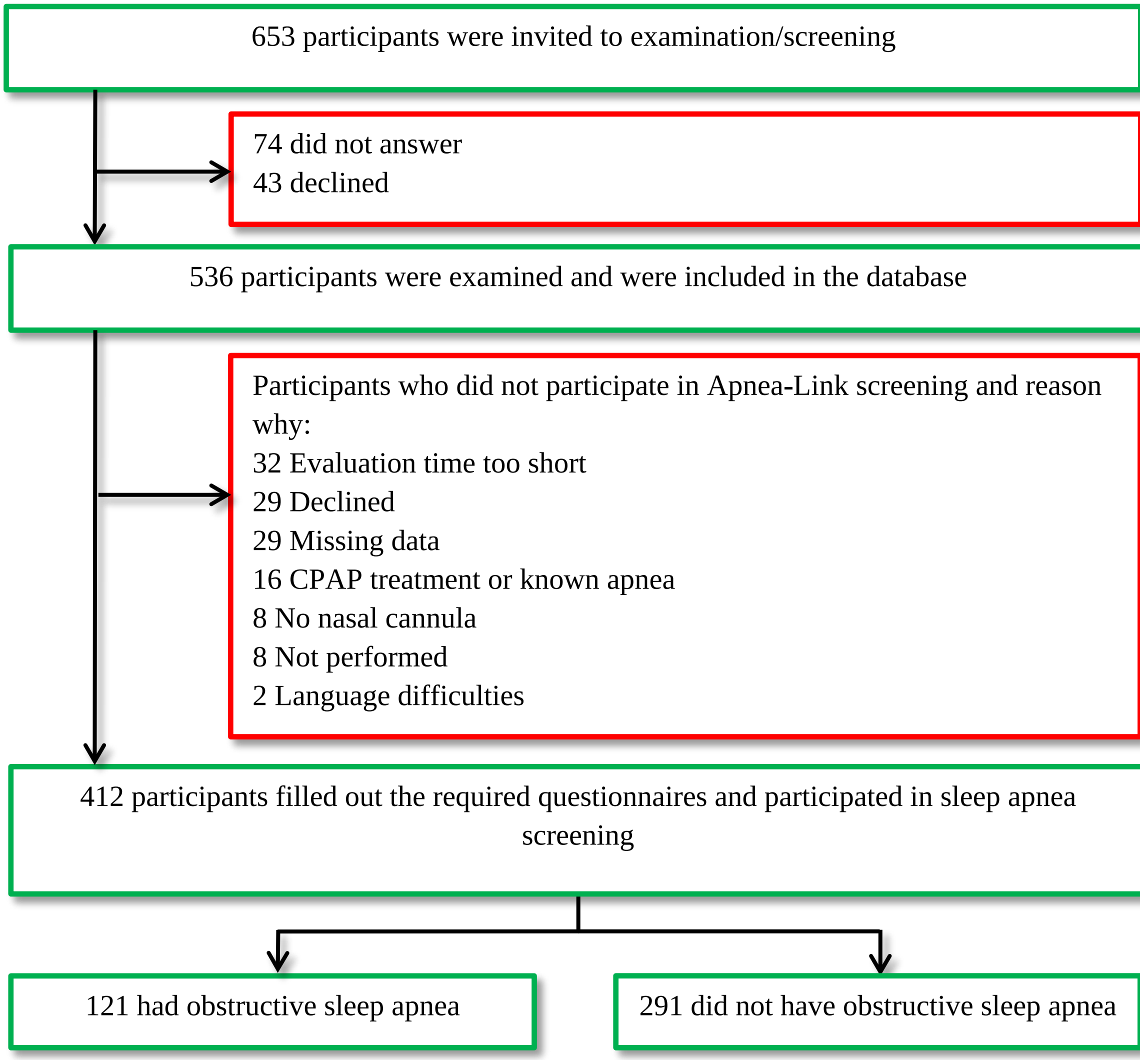

Table 1. Characteristics of study population undergoing sleep apnea screening with ApneaLink				
Variable	All patients (n=412)	OSA (n = 121)	No OSA (n = 291)	P-value
Obesity, %	18.4	32.2	12.7	<0.001
BMI, kg/m^2	27.0 ± 3.8	28.4 ± 4.2	26.4 ± 3.5	<0.001
ESS score	5.5 ± 4.1	6.0 ± 4.5	5.3 ± 3.9	0.117
AHI, no./h	11.7 ± 11.9	26.8 ± 11.3	5.4 ± 3.7	<0.001
ODI, no./h	9.9 ± 10.2	20.8 ± 12.3	5.5 ± 4.3	<0.001
Current smokers, %	6.8	6.6	6.9	0.924
Hypertension, %	82.5	90.1	79.4	0.009
Atrial fibrillation, %	11.4	15.7	9.6	0.077
Diabetes mellitus, %	12.9	15.7	11.7	0.267
Stroke, %	8.5	5.8	9.6	0.203
Depression, %	10.4	9.9	10.7	0.824
Heart failure, %	3.2	5.8	2.1	0.049
Myocardial infarction, %	10.0	12.4	8.9	0.285
Angina pectoris, %	5.3	6.6	4.8	0.459
COPD, %	4.6	3.3	5.2	0.415
Cancer, %	19.7	21.5	18.9	0.547
Asthma, %	4.9	3.3	5.5	0.346
Bypass surgery, %	4.6	5.0	4.5	0.829
PCI, %	8.5	10.7	7.6	0.291

Definition of abbreviations: OSA = obstructive sleep apnea with cutoff at AHI ≥ 15/h; AHI = apnea-hypopnea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; ODI = oxygen desaturation index; PCI = Percutaneous coronary intervention; Means ± SD (standard deviation) are continuous variables expressed as.

Table 2. Variables associated with obstructive sleep apnea in study population*			
	OR	95% CI	P-value
Univariate analysis			
Obesity	3.27	1.95-5.46	<0.001
BMI, kg/m^2	1.14	1.08-1.21	<0.001
Heart failure	2.92	0.96-8.87	0.059
Hypertension	2.36	1.22-4.57	0.011
Multivariate analysis			
BMI, kg/m^2	1.13	1.06-1.20	<0.001
Hypertension	1.78	0.90-3.51	0.098

*Definition of abbreviations: OR = odds ratio; CI; confidence interval; BMI = body mass index. *Study population: n = 412.*

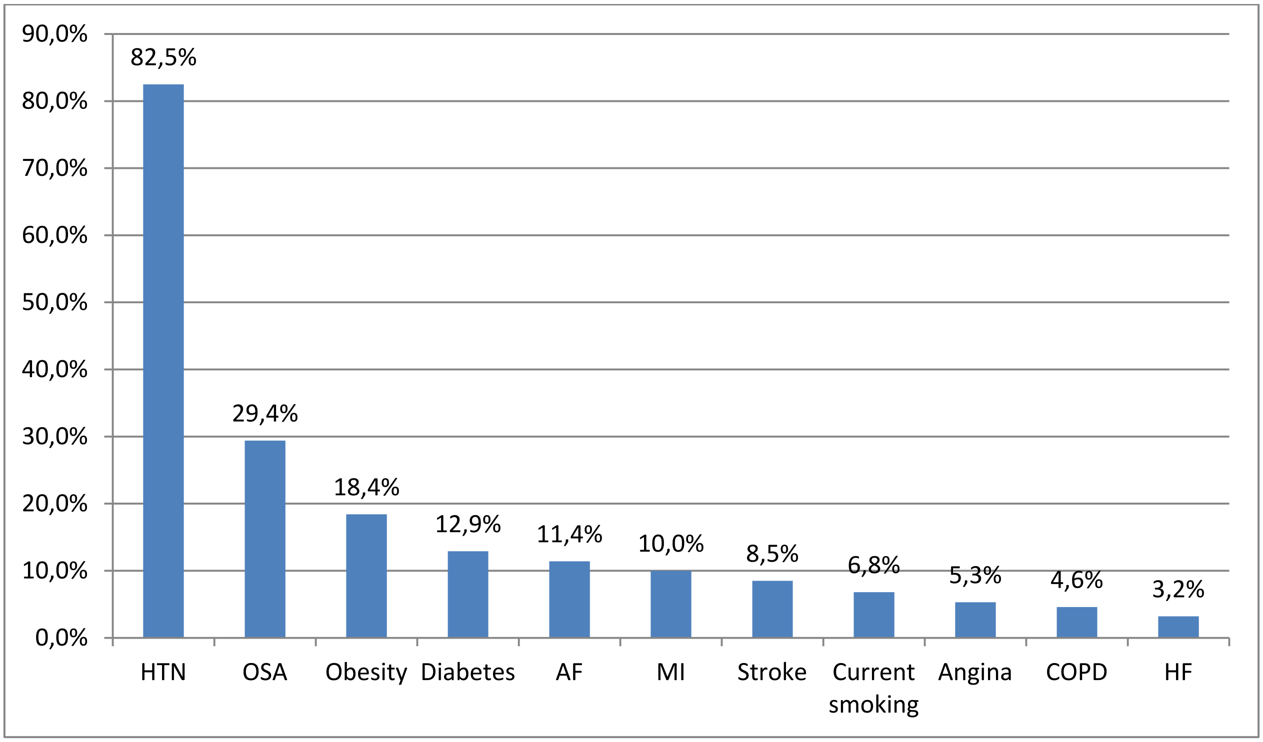

Figure 2. *Occurrence of CVDs, riskfactors for CVDs including OSA in study population (n = 412). Definition of abbreviations: CVDs = cardiovascular diseases; OSA = obstructive sleep apnea with cutoff at AHI ≥ 15; AHI = apnea-hypopnea index; HTN = Hypertension; MI = Myocardial infarction; AF = Atrial fibrillation; COPD = Chronic obstructive pulmonary disease; HF = Heart Failure.*

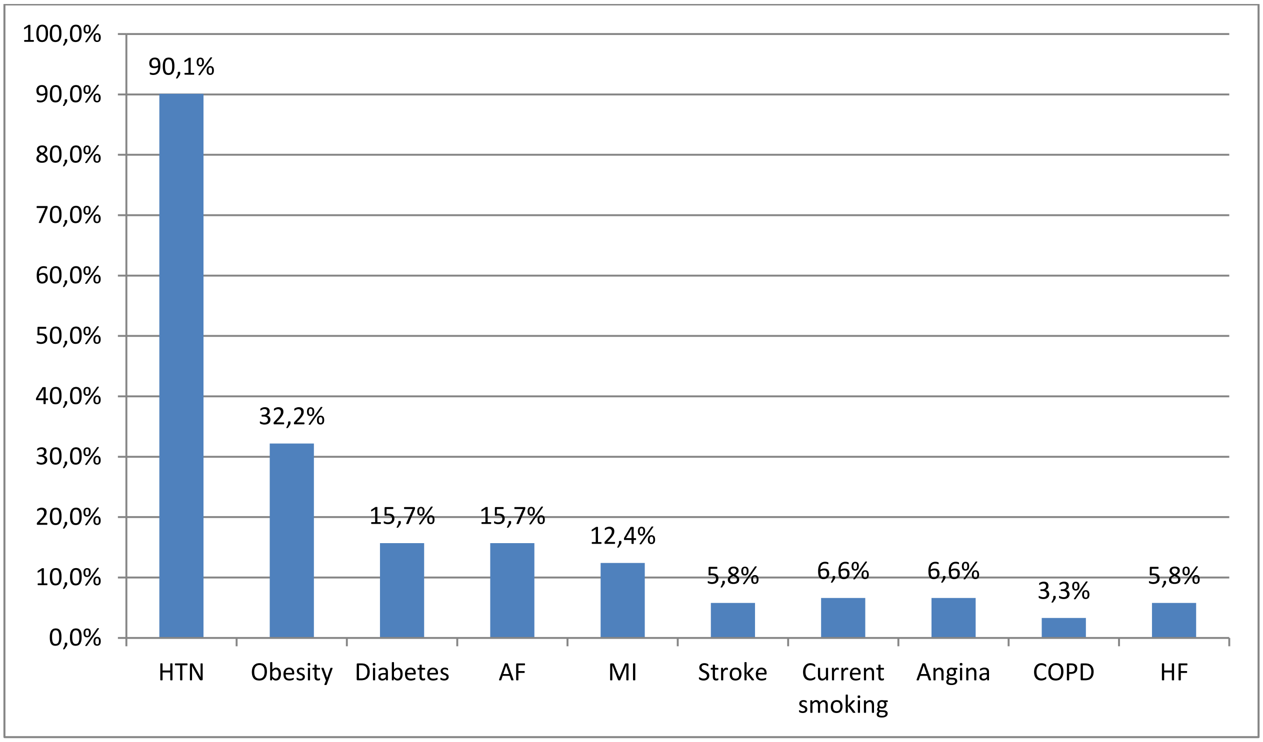

Figure 3. *Occurrence of CVDs, risk factors for CVDs in study population (n = 121) that have OSA. Definition of abbreviations: CVDs = cardiovascular diseases; OSA = obstructive sleep apnea with cutoff at AHI ≥ 15; AHI = apnea-hypopnea index; HTN = Hypertension; MI = Myocardial infarction; AF = Atrial fibrillation; COPD = Chronic obstructive pulmonary disease; HF = Heart Failure.*

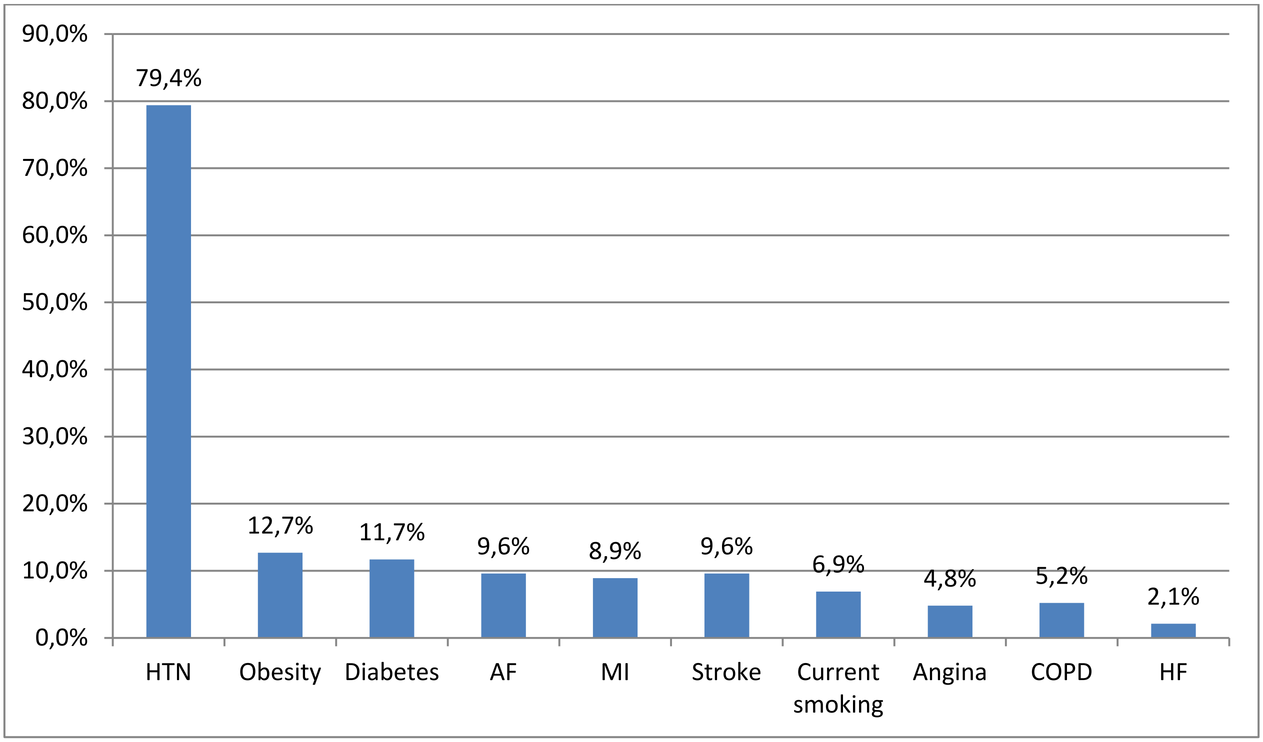

Figure 4. *Occurrence of CVDs, risk factors for CVDs in study population (n = 291) that do not have OSA. Definition of abbreviations: CVDs = cardiovascular diseases; OSA = obstructive sleep apnea with cutoff at AHI ≥ 15; AHI = apnea-hypopnea index; HTN = Hypertension; MI = Myocardial infarction; AF = Atrial fibrillation; COPD = Chronic obstructive pulmonary disease; HF = Heart Failure.*

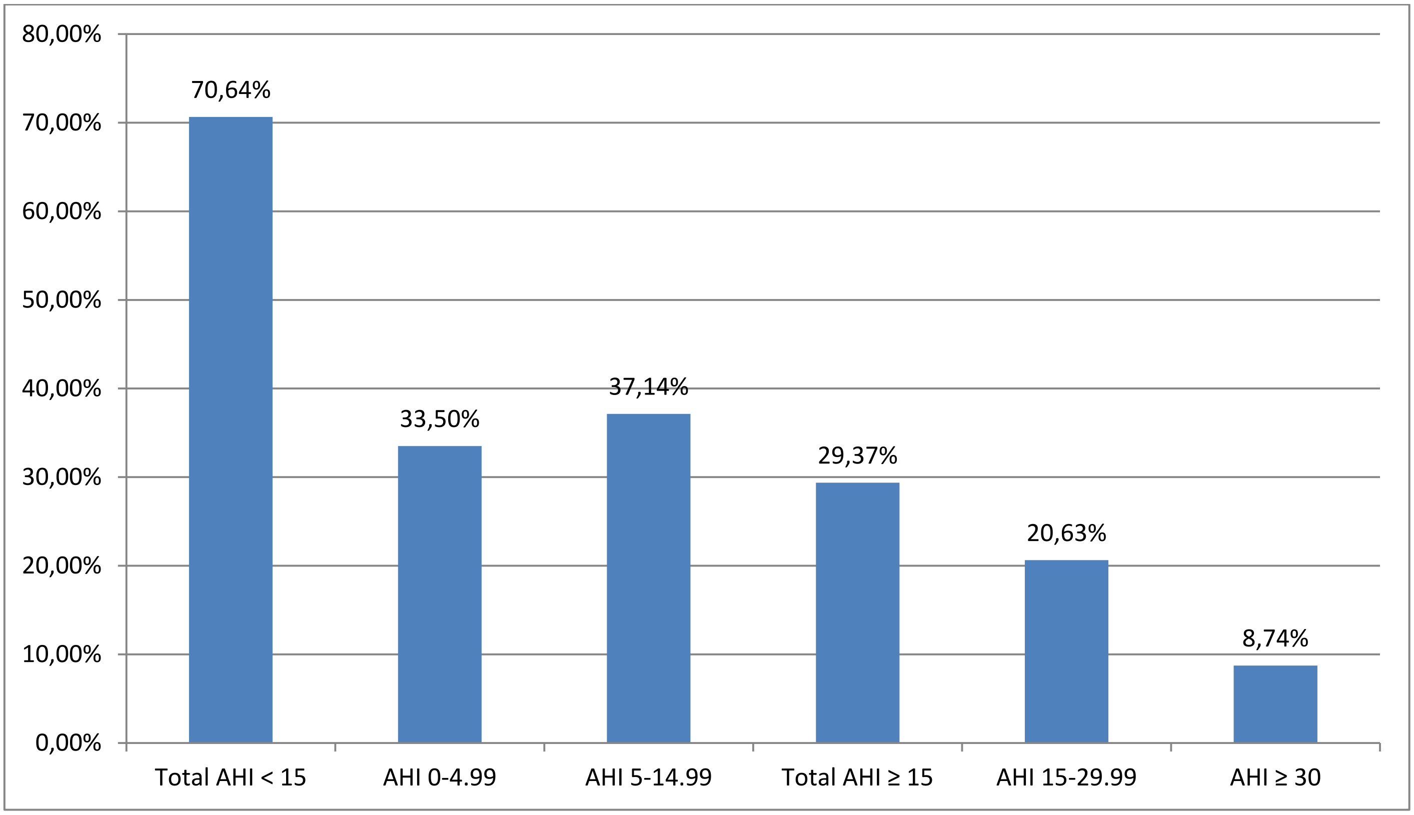

***Figure 5**. AHI levels in study population n=412. Definition of abbreviations: AHI = apnea-hypopnea index*.

Table 3. Characteristics of study population with severe obstructive sleep apnea				
Variable	All patients (n=412)	Severe OSA (n = 36)	No severe OSA (n = 376)	P-value
Obesity, %	18.4	41.7	16.2	<0.001
BMI, kg/m^2	27.0 ± 3.8	29.9 ± 5.0	26.7 ± 3.6	<0.001
ESS score	5.5 ± 4.1	6.4 ± 4.4	5.5 ± 4.1	0.202
AHI, no./h	11.7 ± 11.9	41.0 ± 10.3	8.9 ± 7.5	<0.001
ODI, no./h	9.9 ± 10.2	31.5 ± 15.9	8.0 ± 6.8	<0.001
Current smokers, %	6.8	8.3	6.6	0.701
Hypertension, %	82.5	97.2	81.1	0.015
Atrial fibrillation, %	11.4	25.0	10.1	0.007
Diabetes mellitus, %	12.9	22.2	12.0	0.079
Stroke, %	8.5	5.6	8.8	0.508
Depression, %	10.4	16.7	9.8	0.201
Heart failure, %	3.2	5.6	2.9	0.388
Myocardial infarction, %	10.0	13.9	9.6	0.409
Angina pectoris, %	5.3	8.3	5.1	0.403
COPD, %	4.6	0.0	5.1	0.167
Cancer, %	19.7	19.4	19.7	0.973
Asthma, %	4.9	2.8	5.1	0.544
Bypass surgery, %	4.6	8.3	4.3	0.265
PCI, %	8.5	8.3	8.5	0.971

Definition of abbreviations: Severe OSA = obstructive sleep apnea with cutoff at AHI ≥ 30/h; AHI = apnea-hypopnea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; ODI = oxygen desaturation index; PCI = Percutaneous coronary intervention; Means ± SD (standard deviation) are continuous variables expressed as.

Table 4. Variables associated with severe obstructive sleep apnea in study population*			
	OR	95% CI	P-value
Univariate analysis			
Obesity	3.69	1.80-7.56	<0.001
BMI, kg/m^2	1.21	1.11-1.31	<0.001
Atrial fibrillation	2.97	1.30-6.77	0.010
Hypertension	8.15	1.10-60.47	0.040
Multivariate analysis			
BMI, kg/m^2	1.18	1.09-1.29	<0.001
Atrial fibrillation	2.43	1.02-5.76	0.044
Hypertension	4.89	0.64-37.17	0.125

*Definition of abbreviations: OR = odds ratio; CI; confidence interval; BMI = body mass index. *Study population: n = 412.*

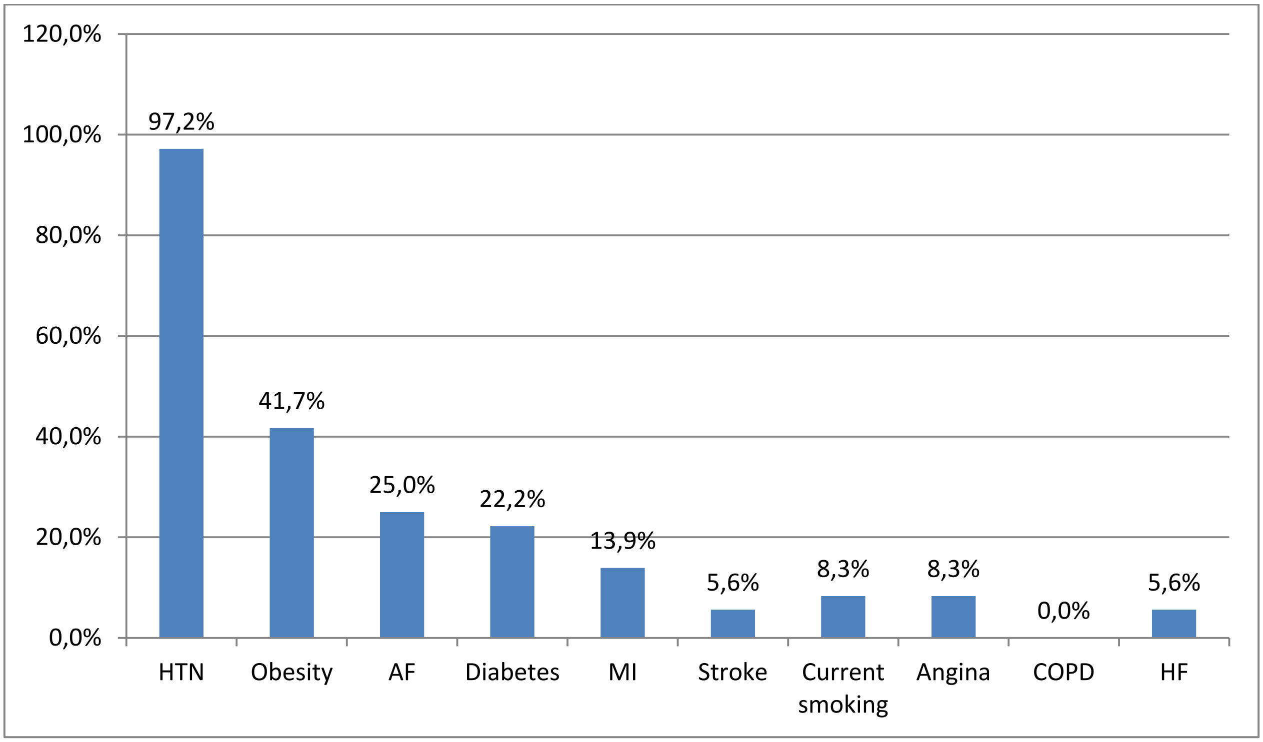

Figure 6. *Occurrence of CVDs, risk factors for CVDs in study population (n = 36) that have severe OSA. Definition of abbreviations: CVDs = cardiovascular diseases; OSA = obstructive sleep apnea with cutoff at AHI ≥ 15; AHI = apnea-hypopnea index; HTN = Hypertension; MI = Myocardial infarction; AF = Atrial fibrillation; COPD = Chronic obstructive pulmonary disease; HF = Heart Failure.*